

Add claims 108-148 as follows:

--108. A method for determining whether a first test protein interacts with a second test protein, said method comprising:

a) providing in a cell:

i) a counterselectable reporter gene operably linked to a first DNA binding protein recognition site or a selectable/ counterselectable reporter gene operably linked to a first DNA binding protein recognition site;

ii) a first fusion gene which expresses a first hybrid protein, said first hybrid protein comprising a test protein covalently bonded to a DNA binding moiety which specifically binds to said DNA binding protein recognition site;

iii) a second fusion gene which expresses a second hybrid protein, said second hybrid protein comprising a test protein covalently bonded to a gene activating moiety; and

b) detecting expression of said reporter gene as a measure of the ability of said first test protein to interact with said second test protein.

109. The method of claim 108, wherein said cell further comprises a second reporter gene.

110. The method of claim 109, wherein said cell further comprises a third reporter gene.

111. The method of claim 109, wherein said second reporter gene is a counterselectable reporter gene.

112. The method of claim 109, wherein said reporter genes are different.

113. The method of claim 109, wherein said reporter genes are identical.

114. The method of claim 109, wherein said second reporter gene is operably linked to a second DNA binding protein recognition site.

115. The method of claim 114, wherein said first and said second DNA binding protein recognition sites are identical.

116. The method of claim 114, wherein said first and said second DNA binding protein recognition sites are different.

117. The method of claim 115, wherein said reporter genes are different.

118. The method of claim 117, wherein said reporter genes are operably linked to different promoters.

119. The method of claim 118, wherein a fusion gene is located on a plasmid.

120. The method of claim 119, wherein said plasmid is a low copy number plasmid.

121. The method of claim 118, wherein said reporter gene is integrated into the genome of said cell or is located on a plasmid.

122. The method of claim 118, wherein said cell is a yeast cell.

123. The method of claim 122, wherein said yeast cell is *S. cerevisiae*.

124. The method of claim 108, wherein said counterselectable reporter gene is selected from the group consisting of URA3, LYS2, CYH2, CAN1, and GAL1.

AI
Cont

10974-239004 / MGH-0792.3

125. The method of claim 108, wherein the number of said DNA binding recognition sites is between 1 and 100.

126. The method of claim 125, wherein the number of said DNA binding recognition sites is between 1 and 20.

127. The method of claim 108, wherein said counterselectable reporter gene is detected as inhibition of growth.

128. The method of claim 108, further comprising isolating a cell which expresses said reporter gene.

129. The method of claim 128, wherein a fusion gene of said isolated cell is amplified.

130. The method of claim 128, wherein a fusion gene of said isolated cell is sequenced.

131. A cell comprising:

a) a counterselectable reporter gene operably linked to a first DNA binding protein recognition site;

b) a first fusion gene which expresses a first hybrid protein, said first hybrid protein comprising a test protein covalently bonded to a DNA binding moiety which specifically binds to said DNA binding protein recognition site; and

c) a second fusion gene which expresses a second hybrid protein, said second hybrid protein comprising a test protein covalently bonded to a gene activating moiety.

132. The cell of claim 131, wherein said cell further comprises a second reporter gene.

133. The cell of claim 132, wherein said second reporter gene is a counterselectable reporter gene.

134. The cell of claim 132, wherein said second reporter gene is operably linked to a second DNA binding protein recognition site.

135. The cell of claim 134, wherein said first and said second DNA binding protein recognition sites are identical.

136. The cell of claim 135, wherein said reporter genes are different.

137. The cell of claim 136, wherein said reporter genes are operably linked to different promoters.

138. A cell comprising:

- i) a first reporter gene operably linked to a first DNA binding protein recognition site; and
- ii) a second reporter gene operably linked to a second DNA binding protein recognition site;

wherein said first and said second DNA binding protein recognition sites are different.

139. The cell of claim 138, wherein a reporter gene is a counterselectable reporter gene.

140. A genetic construct comprising a fusion gene which expresses a hybrid protein, said hybrid protein comprising a test protein covalently bonded to a DNA binding moiety and a C-terminal tag.

141. A method for decreasing the occurrence of false positive interactions between a first test protein and a second test protein, said method comprising

- a) providing in a cell:
 - i) at least two different reporter genes each operably linked to a different promoters having identical binding protein recognition sites;
 - ii) a first fusion gene which expresses a first hybrid protein, said first hybrid protein comprising a test protein covalently bonded to a DNA binding moiety which specifically binds to said DNA binding protein recognition site;
 - iii) a second fusion gene which expresses a second hybrid protein, said second hybrid protein comprising a test protein covalently bonded to a gene activating moiety;
- b) maintaining the level of expression of said first and said second hybrid proteins at physiologically relevant levels;
- c) detecting expression of a reporter gene as a measure of ability of said first test protein to interact with said second test protein.

142. A method for determining whether a test compound affects binding between a first test protein and a second test protein, said method comprising:

- a) providing in a cell:
 - i) a counterselectable reporter gene operably linked to a first DNA binding protein recognition site or a selectable/ counterselectable reporter gene operably linked to a first DNA binding protein recognition site;
 - ii) a first fusion gene which expresses a first hybrid protein, said first hybrid protein comprising a test protein covalently bonded to a DNA bonding moiety which specifically binds to said DNA binding protein recognition site;
 - iii) a second fusion gene which expresses a second hybrid protein, said second hybrid protein comprising a test protein covalently bonded to a gene activating moiety;
- b) contacting said cell with a test compound; and
- c) detecting expression of said reporter gene as a measure of the ability of said compound to effect binding between said first and said second test proteins.

143. The method of claim 142, wherein said counterselectable reporter gene is selected from the group consisting of URA3, LYS2, CYH2, CAN1, and GAL1.

144. The method of claim 142, wherein said first fusion gene or said second fusion gene is derived from a cDNA library.

145. A method for determining whether a first test RNA molecule interacts with a test protein, said method comprising:

a) providing in a cell:

i) a counterselectable reporter gene operably linked to a first DNA binding protein recognition site or a selectable/ counterselectable reporter gene operably linked to a first DNA binding protein recognition site;

ii) a first fusion gene which expresses a first hybrid RNA molecule, said RNA molecule comprising said test RNA molecule covalently bonded to a first non-random RNA molecule;

iii) a second fusion gene which expresses a first hybrid protein, said first hybrid protein comprising a DNA binding moiety which specifically binds to said DNA binding protein recognition site, said DNA binding moiety being covalently bonded to an RNA binding moiety, wherein said RNA binding moiety specifically binds to said non-random RNA molecule;

iv) a third fusion gene which expresses said test protein covalently bonded to a gene activating moiety;

b) detecting expression of said reporter gene as a measure of the ability of said test RNA molecule to interact with said test protein.

146. The method of claim 145, wherein said ability of said first test RNA molecule and said test protein to interact is measured in the presence of a test compound.

147. A method for determining whether a first test RNA molecule interacts with a second test RNA molecule, said method comprising: